Serum Amylase and CRP in Risk Stratification of Pancreas-Specific Complications After Pancreaticoduodenectomy

Lavanniya K. Palani Velu, MRCS[1,2], Colin J. McKay, MD[1], C. Ross Carter, MD[1], Donald C. McMillan, PhD[2], Nigel B. Jamieson, PhD[1,2], and Euan J. Dickson, MD[1]

Affiliations

[1]West of Scotland Pancreatic Unit; Glasgow Royal Infirmary, Glasgow, G31 2ER, UK

[2]The Academic Department of Surgery, University of Glasgow, Glasgow Royal Infirmary, Glasgow, G31 2ER, UK

Contact for correspondence and reprints:

Mr Nigel B Jamieson

Level 2,

New Lister Building,

Glasgow Royal Infirmary,

10-16 Alexandra Parade,

Glasgow G31 2ER

Tel: +44-141-211-8655

E-mail: nigel.jamieson@glasgow.ac.uk

Category: Original article

This work has previously been presented in part at the Great Britain and Ireland Hepato Pancreato Biliary Association Scientific Meeting on the 13th of March 2014.

ABSTRACT

Background

Pancreas-specific complications (PSC), comprising postoperative pancreatic fistula, haemorrhage, and intra-abdominal collections, are drivers of post pancreaticoduodenectomy (PD) morbidity and mortality. Postoperative day 0 (PoD_0) serum amylase ≥ 130 IU/L has been shown to be an objective surrogate of pancreatic texture, a determinant of PSC. This study evaluated serial measurements of C-reactive protein(CRP) to refine PSC risk stratification.

Methods

Consecutive patients undergoing PD between 2008 and 2014, with vascular resection if required and without prior chemoradiotherapy, had serum investigations performed from the pre-operative day until discharge. Receiver operating characteristic (ROC) analysis was used to identify a threshold value of serum CRP with clinically relevant PSC as an outcome measure up to 30 days post-discharge.

Results

Of 230 patients who were included, 95 (41.3%) patients experienced a clinically relevant PSC. Post-operative day 2 (PoD_2) serum CRP ≥180 mg/L was associated with PSC, prolonged critical care stay, and relaparotomy (all $P \leq 0.05$). Patients with a PoD_0 serum amylase ≥ 130 IU/L who developed a PoD_2 serum CRP ≥ 180 mg/L had a higher incidence of morbidity. Patients were stratified into High, Intermediate and Low risk groups using these markers. The Low-risk category was associated with a Negative Predictive Value of 86.8% for clinically relevant PSC development. There were no mortalities (0/52; 0%) in the Low-risk group, with seven deaths (7/79; 9.4%) in the High-risk group.

Conclusions

A Low-risk profile, (PoD_0 serum amylase <130 IU/L and PoD_2 serum CRP <180 mg/L), may identify patients suitable for safe and early discharge following pancreaticoduodenectomy.

INTRODUCTION

Pancreaticoduodenectomy (PD) remains the preferred resectional procedure for malignant and benign disorders of the pancreatic head and the peri-ampullary region. Although previously associated with high postoperative mortality, service centralisation, innovations in surgical technique and advances in perioperative management have successfully reduced this to 5% or less in high-volume centres.[1, 2] Despite these measures, post-PD morbidity rates remain high at 40–50%.[3, 4]

Development of a postoperative pancreatic fistula (POPF) following pancreatic resection is the most important complication, associated subsequently with post-pancreatectomy haemorrhage (PPH) and intra-abdominal collections (IAC).[5,6] These pancreas-specific complications (PSC), a composite term, contribute to severe postoperative morbidity and potentially perioperative mortality.[7]

A soft pancreatic remnant, a small pancreatic duct, along with a high intra-operative blood loss are major risk factors for POPF.[8] These risk factors have been aggregated into a Fistula Risk Score (FRS) which was validated in independent cohorts.[9] The present authors have previously shown that raised serum amylase on the night of surgery (postoperative day 0 [PoD_0]) serves potentially as an objective risk factor for the development of clinically relevant (CR)-POPF, return to theatre and readmission to a critical care environment.[10] This may add objectivity to the subjective intra-operative assessment of risk components for POPF.

C-reactive protein (CRP), has previously been shown to predict postoperative morbidity following oesophageal, gastric, and colorectal resections.[11, 12] Although evidence exists to support the utility of serum CRP in the prediction of postoperative

morbidity following pancreatic resections, it is less clear if the serial assessment of serum CRP can function as a robust trigger to inform clinical decision making.

This study sought to determine serum CRP levels in the immediate postoperative period, and the relationship between CRP, PoD_0 serum amylase levels and established risk factors for postoperative morbidity following PD, in an effort to optimise risk prediction and individualise patient management.

MATERIALS AND METHODS

Patients

In this prospective study all patients underwent either classical or pylorus-preserving PD (PPPD) in the West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, UK, during a 6-year period (January, 2008 to January, 2014) by one of three surgeons for malignant and benign disease. Resectability for malignant disease was classified in accordance with trial inclusion criteria,[13] and outlined previously.[14]

Prospective Data Collection

Demographic, pathological and therapeutic data were recorded on a prospective database populated from a combination of electronic patient records, preoperative imaging and anaesthetic charts. Preoperative clinical data included age, sex, body mass index (BMI), preoperative biliary drainage and serum investigations including amylase, bilirubin and CRP. The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) physiology score was calculated as an objective measure of co-morbidity and preoperative physiology.[15] Preoperative CT images were assessed to calculate pancreatic duct diameter at the line of transection of the pancreas anterior to the portal vein.

Intra-operative data collection included ASA status, reconstruction technique and texture of the pancreatic remnant. Postoperatively the specimens were dichotomised into either pancreatic ductal adenocarcinoma (PDAC) and chronic pancreatitis or other pathology (including ampullary carcinoma, cholangiocarcinoma, duodenal carcinoma, neuroendocrine tumours, and cystic lesions).

Outcome data included length of stay in a critical care environment, (defined as either Level II or III care) and total length of postoperative hospital stay. Data for readmission to Glasgow Royal Infirmary were also recorded. All postoperative complications were prospectively recorded up to 30 days following discharge and graded through detailed weekly consensus discussion by the three operating pancreatic surgeons according to the International Study Group of Pancreatic Surgery (ISGPS) classifications and the Dindo-Clavien classification. [16-18]. Mortality was recorded at 30 and 90-days.

Operative Procedure

Invasive monitoring (central venous, arterial and urinary catheters) and nasogastric tubes (NGTs) were inserted after induction of anaesthesia. All patients received preoperative intravenous (IV) antibiotics as prophylaxis for surgical site infection. A short-acting somatostatin analogue was commenced intra-operatively and continued for 5 days subcutaneously (Octreotide 100 µg, Sun Pharmaceuticals, UK) with a proton-pump inhibitor continued indefinitely. The operative steps of PD and histological analysis were performed as described previously.[14] The extent of resection remained constant during this study. With regards to resections for malignant disease, lesions within the uncinate process or those sited medially would undergo an “artery first” exploration to determine arterial involvement, whereas lesions at the neck underwent an early dissection of the hepaticoduodenal ligament to ensure proximal clearance. Short segment (<180°) venous involvement was managed by en bloc resection and primary anastomosis if necessary.

Pancreatic transection was performed with scalpel, ultrasonic scalpel or diathermy depending on operator preference. The pancreatic remnant was anastomosed using a dual-layer, duct-to-mucosa technique either to jejunum (pancreaticojejunostomy,

[PJ]) or stomach (pancreaticogastrostomy, [PG]). The choice of PJ or PG anastomosis was based on surgeon preference and not allocated according to risk of postoperative complications. Over the study period there was a trend to increased use of PG formation. Pancreatic duct stents were not routinely used. Absorbable synthetic monofilament sutures (Biosyn^{TM}, Covidien) were used for both techniques, with 4/0 sutures for the PJ and 3/0 sutures for the PG. Hepaticojejunostomy and gastrojejunostomy were performed in a standard fashion. At the end of the procedure, one or two non-suction drains were routinely placed adjacent to the pancreatic and biliary anastomosis. The stump of the gastro-duodenal artery was not covered routinely.

Perioperative Management

In the immediate postoperative period all patients were admitted to the surgeon-led SHDU (Level II care). Patients requiring a higher level of care were admitted to the Intensive Care Unit (Level III).

Perioperative care of patients was directed by the operating surgeon. Serum laboratory measurements were performed daily from the pre-operative day until discharge. Patients were allowed sips of clear fluid from the night of surgery with oral intake increased as tolerated. Parenteral nutrition was not instituted routinely. Invasive monitoring was ceased based upon the patients clinical progress. Practice at this institution favours routine drain placement with early removal on the morning of PoD_1 based on measurement of PoD_0 serum amylase.

Management of suspected POPF included antibiotics, image-guided percutaneous drainage, or surgical exploration with extensive peripancreatic drainage or completion pancreatectomy. Over the study period there was a trend towards re-laparotomy and establishing extensive peripancreatic drainage if patients required a

return to theatre. IACs were diagnosed on the basis of clinical observations, and serum investigations, with cross-sectional imaging confirmation. Management involved antibiotics, percutaneous drainage and if necessary, surgical exploration and open drainage. PPH was usually managed with blood transfusion and early angiography with or without coil embolisation or vascular stenting. Endoscopy or re-laparotomy was reserved for patients where angiography did not provide adequate haemostasis.

Definitions of Outcome Measures

The upper normal limit for serum amylase at this institute is 100 IU/L. The upper normal limit for serum CRP is 10mg/L. A drain fluid amylase three times the serum amylase on or after PoD_3 was diagnostic of POPF in accordance with ISGPS definitions.[17]

Intra-abdominal collections (IAC) were defined as any major intra-abdominal fluid collection found on cross-sectional imaging, associated with any of the following: raised inflammatory markers, pyrexia, contiguous drain or wound discharge, or increasing abdominal pain. Post-pancreatectomy haemorrhage was defined by the ISGPS.[18] PSC is a composite term capturing POPF, PPH, or IAC. Patients who experienced more than one PSC had the event of greater severity recorded as the PSC, and the event of lesser severity recorded in the appropriate complication category (POPF, IAC or PPH). Complications of Dindo-Clavien Grade II and greater[16] were classed as CR as were complications graded as ISGPS Grades B or C.

Statistical Analysis

Continuous data are presented as a median (range). Categorical variables were compared using the χ^2 test. The Mann-Whitney *U* test was used to compare continuous variables between two groups while the Kruskal-Wallis test was used to compare between multiple groups. The diagnostic accuracy of serum CRP in predicting adverse postoperative outcomes was assessed with Receiver Operating Characteristic (ROC) analysis.

Univariable binary logistic regression analysis with calculation of odds ratios (OR) and 95% confidence intervals (CI) was used to explore the association between demographic, perioperative clinicopathological factors, including PoD_0 serum amylase and the risk of complications, in particular PSC. Multivariable binary logistic regression analysis was performed on variables showing a significant association on univariable analysis ($P<0.05$). Backward stepwise regression was used starting with a saturated model and variables with a $P>0.1$ excluded at each step until no more variables could be excluded. List-wise deletion was performed in cases with missing data. Statistical significance was set at $P<0.05$. All statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, NY).

RESULTS

Clinicopathological Characteristics of the Study Cohort

230 patients underwent PD in the study period. Table 1 summarises the cohort's demographic, operative, pathologic and treatment characteristics. None of the patients received pre-operative chemoradiotherapy. Median length of drain maintenance was 3 days (IQR 2 - 8 days).

Postoperative Complications

The complication profile of the study cohort is detailed in Table 1. The overall complication rate was 69.1% (Dindo-Clavien grades I-V) with the complication rate graded Dindo-Clavien II and higher equal to 57.8%. Ninety-five (41.3%) patients experienced at least one CR-PSC. Twenty-two patients (9.6%) experienced a chyle leak; the majority of these patients also experienced a CR-PSC. Thirteen patients (5.7%) experienced a biliary fistula, the majority of whom did not require a postoperative intervention.

Thirty-one patients (13.5%) required a re-laparotomy; of these 5 patients (2.2%) required a completion pancreatectomy. One patient (0.4%) returned to theatre for re - laparotomy and arrest of haemorrhage from the liver bed, and one patient returned to theatre for a washout and re-suturing of a dehisced wound. Twenty-four patients (10.4%) returned to theatre for a laparotomy, and establishment of wide peripancreatic drainage for source control of sepsis.

Five (2.2%) deaths occurred as a consequence of PPH and associated complications, two (0.9%) as a result of infected IACs, two (0.9%) as a result of

multi-organ failure and one (0.5%) following a postoperative myocardial infarction. Nine of the ten patients (90%) who died developed ISGPF Grade C POPF.

CRP, Pancreas-Specific Complications, Length of Stay and Mortality

Serial serum CRP measurements of patients who developed clinically relevant complications were compared to those who did not experience a complication (Supplementary Table 1). Patients who developed CR-POPF or CR-PSC had a higher median serum CRP from PoD_2. The influence of PoD_0 serum amylase and texture of the pancreatic remnant on the serial expression of serum CRP is illustrated in Supplementary Figure 1.

ROC analysis determined threshold values of CRP associated with CR-PSC (Figure 1A) and CR-POPF (Figure 1B)**.** A PoD_2 CRP of 180mg/L was most closely associated with CR-PSC (AUC=0.648, 95%CI: 0.58-0.72, sensitivity 81.5%, specificity 40.3%, negative predictive value [NPV] of 75.3% for PSC, *P*<0.001) while a PoD_2 CRP of 230mg/L was most closely associated with CR-POPF (AUC=0.682, 95%CI: 0.60–0.76, sensitivity 61.1%, specificity 61.9%, *P*<0.001).

Patients with a PoD_2 CRP≥180mg/L were more likely to develop clinically relevant PSC, POPF, IAC, PPH, require invasive postoperative intervention or relaparotomy (All *P*<0.05) (Table 2). There was a trend towards higher 90-day mortality rate associated with a PoD_2 CRP≥180mg/L (5.7% vs. 1.4% , *P*=0.132). PoD_2 CRP ≥180mg/L was not associated with non-pancreatic complications including cardiorespiratory, or wound infections. Increasing severity of Dindo-Clavien graded PSC was associated with a rise in median PoD_2 serum CRP (Supplementary Figure 2)**.**

Prediction of Clinically Relevant Pancreas-Specific Complications

The relationships between preoperative characteristics, intra-operative factors, post-operative biochemical markers and the development of CR-PSCs are shown in Supplementary Table 2**.** Significant univariable factors included small pancreatic duct, soft pancreatic texture, PoD_0 amylase>130IU/L and PoD_2 CRP ≥180mg/L (all *P*<0.05).

On multivariable analysis, soft pancreatic texture, PoD_0 amylase>130IU/L and PoD_2 CRP ≥180mg/ were independent predictors of CR-PSC (Table 3).

Predictors of Postoperative Serum CRP levels

Univariable logistic regression determined BMI>25 kg/m^2, pancreatic duct ≤ 3mm, soft pancreatic remnant, non-PDAC/chronic pancreatitis pathology, serum bilirubin >250 mmol/L and PoD_0 serum amylase ≥130 IU/L as factors associated with a PoD_2 CRP≥180 mg/L (all P<0.05) (Supplementary Table 3). When included in the multivariable model, only small pancreatic duct and PoD_0 serum amylase≥130 IU/L were independent predictors.

Objective risk stratification

In order to simplify post – PD risk stratification, patients were grouped into low, intermediate and high-risk categories for developing CR-PSC according to PoD_0 serum amylase and PoD_2 serum CRP as follows; **Low-risk**: PoD_0 serum amylase <130 IU/L and PoD_2 CRP <180 mg/L (n=52 [22.6%]). **High-risk**: PoD_0 serum amylase ≥130 IU/L and PoD_2 CRP ≥180mg/L (n=79 [34.3%]). **Intermediate-risk**: PoD_0 serum amylase<130 IU/L and PoD_2 CRP ≥180mg/L ***or*** PoD_0 serum amylase≥130 IU/L and PoD_2 CRP **<** 180mg/L (n=83 [36.1%]) (Supplementary Table 4). The High and Intermediate risk groups included significantly more patients with soft textured glands, small pancreatic ducts, and other pathology.

The High-risk group identified patients at an elevated risk of CR-PSC when compared to the Intermediate-risk group. Moreover, there was a trend towards an increase in the 90-day mortality rate (8.9% vs. 2.4%) associated with the High compared to Intermediate risk group with no deaths occurring in the Low-risk group (Figure 2). Likewise the Intermediate-risk group experienced a significantly worse complication profile compared to the Low-risk group, with a greater frequency of CR-PSC, POPF, and more frequent invasive postoperative interventions.–Furthermore, increasing risk category was associated with lengths of hospital stay beyond 15 days and critical care stay beyond 7 days.

The Low-risk category was associated with a negative predictive value (NPV) of 86.5% for the development of CR-PSC with a negative likelihood ratio (LR-) of 0.19 compared the intermediate/High-Risk categories. The High-risk category had a PPV of 65.8% for the development of CR-PSC with a LR+ of 2.35 compared to the rest of the cohort. This risk categorisation tool remained a predictor of PSC following stratification by remnant gland texture (Figure 2).

DISCUSSION

The present study shows that, in addition to PoD_0 serum amylase, an elevated PoD_2 serum CRP is associated with clinically relevant pancreas-specific complications. Taken together, these simple serum investigations can stratify the risk for CR-PSC following PD. Incorporating intra-operative data of the organ response (as assessed by PoD_0 serum amylase) and the host response to the surgical procedure (PoD_2 serum CRP), the current analysis determined three risk groups with an increasing probability of developing CR-PSC. Most significantly, this analysis demonstrated a high NPV (86.8%) for CR-PSC for patients in the Low-risk category.

The rate of significant complications and mortality after PD in the present cohort is broadly in keeping with established literature.[19] POPF is not the only determinant of severe morbidity post-PD. Overall morbidity or CR-PSC that can increase mortality and translate into prolonged inpatient hospital stay, readmission and greater economic burden should become the focus of risk stratification following PD. PSC represents a useful composite term capturing not only overt POPF but also major consequences of fistulae that were not clinically obvious.[20]

The utility of PoD_0 serum amylase as an objective marker to identify patients with a low-risk of a CR-POPF (ISGPS B/C) has been demonstrated previously.[10] A recent study revealed similar results with an elevated PoD_1 serum amylase as an independent predictor of POPF.[21] In an effort to further refine risk stratification post-PD, the utility of postoperative serum CRP was investigated as a tool to identify patients potentially suitable for rapid recovery and safe, early discharge.

The association between a raised postoperative serum CRP and clinically relevant anastomotic leakage has been demonstrated in colorectal and oesophageal surgery.[11, 12] A study of serum CRP in patients who had undergone PD

recommended a PoD_4 serum CRP cut-off of 140mg/L to predict general inflammatory complications.[22] Uemura *et al* proposed that PoD_4 CRP of 156mg/L and non-serous fluid in abdominal drains was associated with CR-POPF,[23] while Ansorge *et al* utilised a combination of drain amylase and elevated PoD_3 serum CRP.[24] The latter study provided strong evidence for serum CRP predicting postoperative complications yet was limited as intra-operative predictors of POPF including pancreatic texture and duct size were not considered.

A risk stratification tool is of clinical utility if it has potential to impact patient management. A risk-stratified perioperative management algorithm could be constructed utilising PoD_0 serum amylase and PoD_2 serum CRP. Patients in the Low-risk category could be considered suitable for cessation of invasive monitoring, drain removal and rapid step-down from a level II critical care environment. The clinician would also be aware of the increased risk of latent CR-PSC in the Intermediate and High-risk groups, informing clinical decision making beyond PoD_2.

The controversy regarding drainage continues to impact the perioperative management of patients undergoing PD. Concern has arisen regarding a standardised no-drain policy, notably, in a study by Correa-Gallego *et al*, where mortality was increased (1% vs. 3%, P=0.02) when routine drainage was eliminated following PD.[25] Furthermore, a recent randomised multicenter trial concluded that elimination of drainage increases severity and frequency of complications, and may have contributed to increased mortality.[26] If absence of drainage increases mortality risk, then a compromise may be that of routine drainage in all PDs followed by selective, early and safe drain removal in order to minimise drain-associated morbidity. Selective drain placement is an alternative strategy, however, this is based on subjective assessment of pancreatic texture.[8].

Pancreatic texture has previously been identified as the principal determinant of an elevated CRP following PD.[27] Independent factors related to an elevated PoD_2 CRP in this study were a small pancreatic duct, and PoD_0 serum amylase≥130IU/L. Notably neither preoperative jaundice nor biliary drainage correlated with postoperative CRP suggesting that bacteraemia related to biliary tract obstruction or manipulation was not an important factor. The mechanism underlying hyperamylaesemia post-PD also remains unclear. While this may represent extravasation of pancreatic secretions with systemic absorption; postoperative hyperamylaesemia could potentially represent pancreatitis of the normal pancreatic remnant, which subsequently predisposes to anastomotic failure.[28] Obstruction of the pancreatic duct at the anastomosis due to haemorrhage, or suture placement, are also potential explanations.

In patients with a high PoD_0 serum amylase, there was a failure of the expected normalisation of CRP after 48hrs, with the majority of patients who subsequently developed a CR-PSC maintaining a raised CRP by PoD_6. While this could indicate a proportionate rise of serum CRP in the context of post-PD pancreatitis, an elevation of PoD_2 serum CRP beyond the 180mg/L threshold in patients with a low PoD_0 serum amylase could indicate a disproportionate immune response to the surgical insult of a PD.

Traditionally, a rise in serum CRP is considered to be due to, rather than the cause of postoperative complications. Emerging evidence suggests that CRP may play a role in bridging the innate and adaptive immune systems by assisting complement-binding and phagocytosis.[29] High levels depress T-lymphocyte function, exaggerate the stress response and hyperglycaemia[30] with the latter factors vital in promoting bacterial growth and development of infective postoperative complications.[31]

Limitations

Despite the retrospective nature of the analysis, the data generated through examination of routine serum biochemical tests are informative. All patients in this cohort received octreotide as prophylaxis for POPF. Evidence for the utility of somatostatin analogues in pancreatic surgery is conflicting.[32, 33] However, based on best available evidence, octreotide is administered as part of the peri-pancreatectomy management strategy at this and other institutions.[34] Decreasing diameter of the pancreatic duct is associated with increasing risk of CR-POPF and post-PD morbidity.[8] However the size of the present cohort precluded the analysis of this factor. A recent study demonstrated that POD_1 amylase <600U/L was associated with absence of POPF.[35] This would suggest that drain amylase levels on PoD_1 and PoD_3 could enhance PSC risk prediction. However, the measurement of drain amylase levels was often limited by haemolysis in the majority of patients. This study was unable to provide data with regards to the day when the CR-PSC became clinically apparent, limiting the analysis with regard to the time-lag between availability of risk-stratification and diagnosis of CR-PSC. Delayed gastric emptying (DGE), was poorly recorded prior to 2012, and was not included in the analysis. Compared to assessment based on pre- and intra-operative factors alone, the current study is limited as scoring requires review at PoD_2. However, this reflects an opportune time point for informed, clinically triggered postoperative management decisions regarding drain management, nutrition, and critical care step-down. Finally, an external cohort was not utilised for validation.

In conclusion, the results of the present study suggest that routine, postoperative measurements of serum amylase and CRP can provide a risk stratification tool for clinically relevant pancreas-specific complications following pancreaticoduodenectomy.

ACKNOWLEDGEMENTS

The authors thank the following members of the West of Scotland Pancreatic Unit: Dr. Hedvig Karteszi for diagnostic imaging and Clinical Nurse Specialist Sr. Elspeth Cowan and Audit Secretary Diane Stewart for follow-up data.

References

1. Bentrem DJ, Yeh JJ, Brennan MF, Kiran R, Pastores SM, Halpern NA, Jaques DP, Fong Y. Predictors of intensive care unit admission and related outcome for patients after pancreaticoduodenectomy. *J Gastrointest Surg* 2005;**9**(9): 1307-1312.
2. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg* 1995;**222**(5): 638-645.
3. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, Clavien P-A. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. *Ann Surg* 2006;**244**(6): 931-937; discussion 937-939.
4. Standop J, Glowka T, Schmitz V, Schäfer N, Overhaus M, Hirner A, Kalff JC. Operative re-intervention following pancreatic head resection: indications and outcome. *J Gastrointest Surg* 2009;**13**(8): 1503-1509.
5. Grützmann R, Rückert F, Hippe-Davies N, Distler M, Saeger H-D. Evaluation of the International Study Group of Pancreatic Surgery definition of post-pancreatectomy hemorrhage in a high-volume center. *Surgery* 2012;**151**(4): 612-620.
6. Schulick RD. Complications after pancreaticoduodenectomy: intraabdominal abscess. *J Hepatobiliary Pancreat Surg* 2008;**15**(3): 252-256.
7. Kawai M, Yamaue H. Analysis of clinical trials evaluating complications after pancreaticoduodenectomy: a new era of pancreatic surgery. *Surg Today* 2010;**40**(11): 1011-1017.
8. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 2013;**216**(1): 1-14.
9. Miller BC, Christein JD, Behrman SW, Drebin JA, Pratt WB, Callery MP, Vollmer CM. A multi-institutional external validation of the fistula risk score for pancreatoduodenectomy. *J Gastrointest Surg* 2014;**18**(1): 172-179; discussion 179-180.
10. Palani Velu LK, Chandrabalan VV, Jabbar S, McMillan DC, McKay CJ, Carter CR, Jamieson NB, Dickson EJ. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. *HPB (Oxford)* 2014;**16**(7): 610-619.
11. Warschkow R, Tarantino I, Ukegjini K, Beutner U, Müller SA, Schmied BM, Steffen T. Diagnostic study and meta-analysis of C-reactive protein as a predictor of postoperative inflammatory complications after gastroesophageal cancer surgery. *Langenbecks Arch Surg* 2012;**397**(5): 727-736.
12. Platt JJ, Ramanathan ML, Crosbie RA, Anderson JH, McKee RF, Horgan PG, McMillan DC. C-reactive protein as a predictor of postoperative infective complications after curative resection in patients with colorectal cancer. *Ann Surg Oncol* 2012;**19**(13): 4168-4177.
13. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW, Cancer ESGfP. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;**304**(10): 1073-1081.
14. Jamieson NB, Foulis AK, Oien KA, Going JJ, Glen P, Dickson EJ, Imrie CW, McKay CJ, Carter R. Positive mobilization margins alone do not influence survival following pancreatico-duodenectomy for pancreatic ductal adenocarcinoma. *Ann Surg* 2010;**251**(6): 1003-1010.
15. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991;**78**(3): 355-360.
16. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;**250**(2): 187-196.
17. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M, Definition ISGoPF. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;**138**(1): 8-13.
18. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007;**142**(1): 20-25.
19. Correa-Gallego C, Brennan MF, D'Angelica MI, DeMatteo RP, Fong Y, Kingham TP, Jarnagin WR, Allen PJ. Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. *J Am Coll Surg* 2012;**215**(5): 616-621.
20. Pratt WB, Callery MP, Vollmer CM. The latent presentation of pancreatic fistulas. *Br J Surg* 2009;**96**(6): 641-649.

21. Cloyd JM, Kastenberg ZJ, Visser BC, Poultsides GA, Norton JA. Postoperative serum amylase predicts pancreatic fistula formation following pancreaticoduodenectomy. *J Gastrointest Surg* 2014;**18**(2): 348-353.
22. Welsch T, Frommhold K, Hinz U, Weigand MA, Kleeff J, Friess H, Büchler MW, Schmidt J. Persisting elevation of C-reactive protein after pancreatic resections can indicate developing inflammatory complications. *Surgery* 2008;**143**(1): 20-28.
23. Uemura K, Murakami Y, Sudo T, Hashimoto Y, Kondo N, Nakagawa N, Sasaki H, Ohge H, Sueda T. Indicators for proper management of surgical drains following pancreaticoduodenectomy. *J Surg Oncol* 2014.
24. Ansorge C, Nordin JZ, Lundell L, Strömmer L, Rangelova E, Blomberg J, Del Chiaro M, Segersvärd R. Diagnostic value of abdominal drainage in individual risk assessment of pancreatic fistula following pancreaticoduodenectomy. *Br J Surg* 2014;**101**(2): 100-108.
25. Correa-Gallego C, Brennan MF, D'angelica M, Fong Y, Dematteo RP, Kingham TP, Jarnagin WR, Allen PJ. Operative drainage following pancreatic resection: analysis of 1122 patients resected over 5 years at a single institution. *Ann Surg* 2013;**258**(6): 1051-1058.
26. Van Buren G, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, Vollmer C, Velanovich V, Riall T, Muscarella P, Trevino J, Nakeeb A, Schmidt CM, Behrns K, Ellison EC, Barakat O, Perry KA, Drebin J, House M, Abdel-Misih S, Silberfein EJ, Goldin S, Brown K, Mohammed S, Hodges SE, McElhany A, Issazadeh M, Jo E, Mo Q, Fisher WE. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Ann Surg* 2014;**259**(4): 605-612.
27. Murakami Y, Uemura K, Hayasidani Y, Sudo T, Hashimoto Y, Nakagawa N, Ohge H, Sueda T. A soft pancreatic remnant is associated with increased drain fluid pancreatic amylase and serum CRP levels following pancreatoduodenectomy. *J Gastrointest Surg* 2008;**12**(1): 51-56.
28. Ansorge C, Regner S, Segersvärd R, Strömmer L. Early intraperitoneal metabolic changes and protease activation as indicators of pancreatic fistula after pancreaticoduodenectomy. *Br J Surg* 2012;**99**(1): 104-111.
29. Sander LE, Sackett SD, Dierssen U, Beraza N, Linke RP, Müller M, Blander JM, Tacke F, Trautwein C. Hepatic acute-phase proteins control innate immune responses during infection by promoting myeloid-derived suppressor cell function. *J Exp Med* 2010;**207**(7): 1453-1464.
30. Peisajovich A, Marnell L, Mold C, Du Clos TW. C-reactive protein at the interface between innate immunity and inflammation. *Expert Rev Clin Immunol* 2008;**4**(3): 379-390.
31. Ramos M, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, Rogers SO. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. *Ann Surg* 2008;**248**(4): 585-591.
32. McMillan MT, Christein JD, Callery MP, Behrman SW, Drebin JA, Kent TS, Miller BC, Lewis RS, Vollmer CM. Prophylactic octreotide for pancreatoduodenectomy: more harm than good? *HPB (Oxford)* 2014;**16**(10): 954-962.
33. Allen PJ, Gönen M, Brennan MF, Bucknor AA, Robinson LM, Pappas MM, Carlucci KE, D'Angelica MI, DeMatteo RP, Kingham TP, Fong Y, Jarnagin WR. Pasireotide for postoperative pancreatic fistula. *N Engl J Med* 2014;**370**(21): 2014-2022.
34. Gurusamy KS, Koti R, Fusai G, Davidson BR. Somatostatin analogues for pancreatic surgery. *Cochrane Database Syst Rev* 2013;**4**: CD008370.
35. Ven Fong Z, Correa-Gallego C, Ferrone CR, Veillette GR, Warshaw AL, Lillemoe KD, Fernández-del Castillo C. Early Drain Removal--The Middle Ground Between the Drain Versus No Drain Debate in Patients Undergoing Pancreaticoduodenectomy: A Prospective Validation Study. *Ann Surg* 2015;**262**(2): 378-383.

Table 1. Demographic, operative, pathological and postoperative outcome characteristics for 230 patients undergoing pancreaticoduodenectomy.

Characteristics		n (%)
Demographics		
Age (years)[1]	≤ 60	100 (43.5)
	> 60	130 (56.5)
Sex	Female	79 (34.4)
	Male	151 (65.7)
BMI (kg/m^2)	< 25	97 (42.2)
	≥ 25	126 (54.8)
Smoking	No	134 (58.3)
	Yes	71 (30.9)
POSSUM Score[2]	≤ 16	114 (49.6)
	> 16	97 (42.2)
ASA	I	30 (13.0)
	II	135 (58.7
	III	35 (15.2)
	IV	2 (0.9)
Bilirubin (mmol/L)	≤ 250	197 (85.7)
	> 250	33 (14.3)
Pre-operative Biliary Drainage	No	129 (56.1)
	Yes	101 (43.9)
Operative		
Procedure	PPPD	69 (30.0)
	Classical	161 (70.0)
Vein Resection	No	193 (83.9)
	Yes	37 (16.1)
Pancreatic Anastomosis	Pancreaticogastrostomy	51 (22.2)
	Pancreaticojejunostomy	176 (76.5)
Pancreatic Texture	Hard	97 (42.2)
	Soft	94 (40.9)
Pancreatic Duct Diameter (mm)	> 3	141 (61.3)
	≤ 3	80 (34.8)
Estimated Blood Loss (ml)[3]	< 1450	121 (56.3)
	≥ 1450	94 (43.7)
Pathology	PDAC	83 (36.1)
	Ampullary adenocarcinoma	41 (17.8)
	Cholangiocarcinoma	31 (13.5)
	Chronic pancreatitis	17 (7.4)
	Neuroendocrine tumor	14 (6.1)
	IPMN	13 (5.7)
	Duodenal adenocarcinoma	12 (5.2)
	Other	18 (7.8)
Postoperative Outcome		
Pancreas-specific Complication[4]	Grade 0 - I	135 (58.7)
	Grade II - V	95 (41.3)
Postoperative Pancreatic Fistula[4]	Grade 0 - I	176 (76.5)
	Grade II - V	54 (23.5)
Intra-abdominal Collection[4]	Grade 0 - I	160 (69.6)
	Grade II - V	70 (30.4)
Post-pancreatectomy Haemorrhage[4]	Grade 0 - I	203 (88.3)
	Grade II - V	27 (11.7)
Cardiorespiratory Complication[4]	Grade 0 - I	181 (78.7)
	Grade II - V	49 (21.3)
Wound infection[4]	Grade 0 - I	194 (84.3)
	Grade II - V	36 (15.7)
Invasive Intervention	No	176 (76.5)
	Yes	54 (23.5)
Reoperation	No	199 (86.5)
	Yes	31 (13.5)
Readmission to Critical Care	No	175 (76.1)
	Yes	47 (20.4)
Length of Stay (days)	Critical Care	7.0 (5.0–10.0)[5]
	Overall	15.0 (11.8–25.0)[5]
Hospital readmission (30-day)		47 (20.4)
Mortality (30-day)		6 (2.6)
Mortality (90-day)		10 (4.3)

[1] Mean age 60 years.
[2] Median POSSUM score was 16.
[3] Median estimated blood loss was 1450ml (IQR 803 - 2000 ml).
[4] Grade refers to the Dindo-Clavien scale of postoperative complications.
[5] Median and interquartile range.
BMI - Body Mass Index, **POSSUM** - Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (median = 16), **PPPD** - Pylorus-preserving pancreaticoduodenectomy, **PDAC** - pancreatic ductal adenocarcinoma, **IPMN** - intraductal papillary mucinous neoplasm, **Other** - miscellaneous tumour types.

Table 2. Relationship between PoD_2 serum CRP and postoperative outcomes following pancreaticoduodenectomy (n = 230).

Category		CRP < 180mg/L N (%) 73 (31.7)	CRP ≥ 180mg/L N (%) 157 (68.3)	*P* [1]
Pancreas-specific complications[2]	Grade 0 – I	55 (75.3)	80 (51.0)	
	Grade II – V	18 (24.7)	77 (49.0)	<0.001
Postoperative pancreatic Fistula[3]	No	61 (83.6)	96 (61.1)	
	Grade A	3 (4.1)	16 (10.2)	
	Grade B	5 (6.8)	28 (17.8)	
	Grade C	4 (5.5)	17 (10.8)	0.007
Intra-abdominal collection[2]	Grade 0 – I	61 (83.6)	99 (63.1)	
	Grade II – V	12 (16.4)	58 (36.9)	0.002
Post-pancreatectomy haemorrhage[3]	No	69 (94.5)	132 (85.4)	
	Grade A	0 (0.0)	2 (1.3)	
	Grade B	3 (4.1)	11 (7.0)	
	Grade C	1 (1.4)	12 (7.6)	0.044
Cardiorespiratory complications[2]	Grade 0 – I	57 (80.3)	124 (78.0)	
	Grade II – V	14 (19.7)	35 (22.0)	0.695
Wound infections[2]	Grade 0 – I	65 (89.0)	129 (82.2)	
	Grade II – V	8 (11.0)	28 (17.8)	0.183
Readmission to critical care	No	62 (84.9)	121 (77.1)	
	Yes	11 (15.1)	36 (22.9)	0.157
Invasive intervention	No	63 (86.3)	113 (72.0)	
	Yes	10 (13.7)	44 (28.0)	0.017
Reoperation	No	68 (93.2)	131 (83.4)	
	Yes	5 (6.8)	26 (16.6)	0.045
Length of stay (days)[4]	Critical Care	6.0 (4.5 – 21.5)	7.0 (5.0 – 10.0)	0.032[5]
	Overall	13.0 (9.0 – 21.5)	16.0 (12.0 – 27.0)	0.002[5]
Readmission (30-day)	No	64 (87.7)	119 (75.8)	
	Yes	9 (12.3)	38 (24.2)	0.038
Mortality (90-day)		1 (1.4)	9 (5.7)	0.132

Pancreas-specific complications includes postoperative pancreatic fistula and/or intra-abdominal collections.
[1] Chi-squared test.
[2] Grade refers to Dindo-Clavien classification of generic complications.
[3] Refers to ISGPS grade. Grades B/C were classed as clinically relevant.
[4] Median, inter-quartile range.
[5] Mann-Whitney *U* test.

Table 3. Multivariable logistic regression analysis for clinically relevant pancreas-specific complications (n = 230).

	Variable	Odds Ratio (95% CI)	*P*
Model A	Pancreatic duct diameter (≤ 3mm)	1.43 (0.71 – 2.85)	0.317
	Pancreatic texture (soft)	3.62 (1.97 – 6.65)	<0.001
Model B	Pancreatic duct diameter (≤ 3mm)	1.19 (0.56 – 2.54)	0.648
	Pancreatic texture (soft)	2.51 (1.23 – 5.11)	0.011
	PoD_0 serum amylase (≥ 130 IU/L)	3.72 (1.84 – 7.53)	<0.001
Model C	Pancreatic duct diameter (≤ 3mm)	1.02 (0.50 – 2.10)	0.947
	Pancreatic texture (soft)	2.36 (1.22 – 4.56)	0.011
	PoD_0 serum amylase (≥ 130 IU/L)	3.17 (1.64 – 6.12)	0.001
	PoD_2 serum CRP (≥ 180 mg/L)	2.39 (1.10 – 5.51)	0.026

Supplementary Table 1. The relationship between serial serum CRP levels and (A) Clinically Relevant Postoperative Pancreatic Fistula and (B) Clinically Relevant Pancreas-specific Complication (n = 230).

	Serum CRP (mg/L)[1]						
	Study Cohort	**Postoperative Pancreatic Fistula**			**Pancreas-Specific Complication**		
Day	**N (%) 230 (100%)**	**Absent N (%) 176 (76.5)**	**Present N (%) 54 (23.5)**	***P*[2]**	**Absent N (%) 135 (58.7)**	**Present N (%) 95 (41.3)**	***P*[2]**
Pre-Op	6 (3 – 16)	6 (3 – 16)	6 (2 – 16)	0.648	6 (3 – 16)	6 (3 – 16)	0.793
0	24 (14 – 40)	24 (13 – 40)	25 (14 – 38)	0.926	24 (13 – 41)	25 (14– 39)	0.961
1	121 (87 – 154)	120 (84 – 153)	123 (104 – 164)	0.115	117 (83– 149)	123 (102 – 165)	0.093
2	**216 (162 – 270)**	**209 (147 – 260)**	**257 (195 – 303)**	**<0.001**	**208 (141 – 247)**	**245 (188 – 289)**	**<0.001**
3	186 (138 – 258)	173 (130 – 245)	232 (182 – 291)	<0.001	169 (121 – 242)	223 (169 – 274)	<0.001
4	148 (92 – 219)	130 (83 – 206)	196 (141 – 272)	<0.001	119 (76 – 202)	177 (129 – 247)	<0.001
5	115 (62 – 199)	103 (55 – 175)	167 (111 – 241)	<0.001	93 (47 – 153)	159 (101 – 225)	<0.001
6	109 (56 – 178)	87 (49 – 167)	170 (103 – 241)	<0.001	78 (43 – 162)	159 (96 – 219)	<0.001
7	107 (57 – 177)	91 (44 – 156)	172 (109 – 248)	<0.001	73 (29 – 129)	167 (105 – 229)	<0.001

[1] Median (Inter-quartile range).
[2] Mann-Whitney *U* test.
Clinically relevant (CR) pancreas-specific complication including CR - POPF, CR - PPH and CR - IAC.

Supplementary Table 2. Univariable predictors of clinically relevant pancreas-specific complications (CR-PSC) in patients undergoing pancreaticoduodenectomy (n = 230).

Variable	OR (95% CI)	*P*
Preoperative factors		
Age (years)		
≤ 60		
> 60	1.10 (0.65 – 1.87)	0.725
Sex		
Female		
Male	1.58 (0.90 – 2.78)	0.113
BMI (kg/m^2)		
< 25		
≥ 25	1.51 (0.88 – 2.60)	0.136
Smoking		
No		
Yes	1.03 (0.58 – 1.84)	0.928
POSSUM Score		
< 16		
≥ 16	1.23 (0.71 – 2.12)	0.464
Bilirubin (mmol/L)		
≤ 250		
> 250	1.06 (0.50 – 2.23)	0.888
Preoperative Biliary Drainage		
No		
Yes	0.66 (0.39 – 1.12)	0.657
ASA		
I - II		
III - IV	0.69 (0.32 – 1.46)	0.325
Intraoperative Factors		
Vein Resection		
No		
Yes	1.25 (0.62 – 2.54)	0.532
Pancreatic Texture		
Hard		
Soft	3.79 (2.07 – 6.95)	<0.001
Pancreatic Duct Diameter (mm)		
> 3		
≤ 3	2.18 (1.25 – 3.82)	0.006
Pancreatic Anastomosis		
Pancreaticogastrostomy		
Pancreaticojejunostomy	1.05 (0.55 – 1.99)	0.885
Estimated blood loss (ml)		
< 1450		
≥ 1450	1.10 (0.64 – 1.90)	0.736
Pathology		
PDAC/ Chronic Pancreatitis		
Other	1.37 (0.81 – 2.34)	0.245
PoD$_0$ Serum Amylase (IU/L)		
< 130		
≥ 130	5.20 (2.88 – 9.40)	<0.001
PoD$_2$ Serum CRP (mg/L)		
< 180		
≥ 180	3.84 (1.84 - 6.59)	<0.001

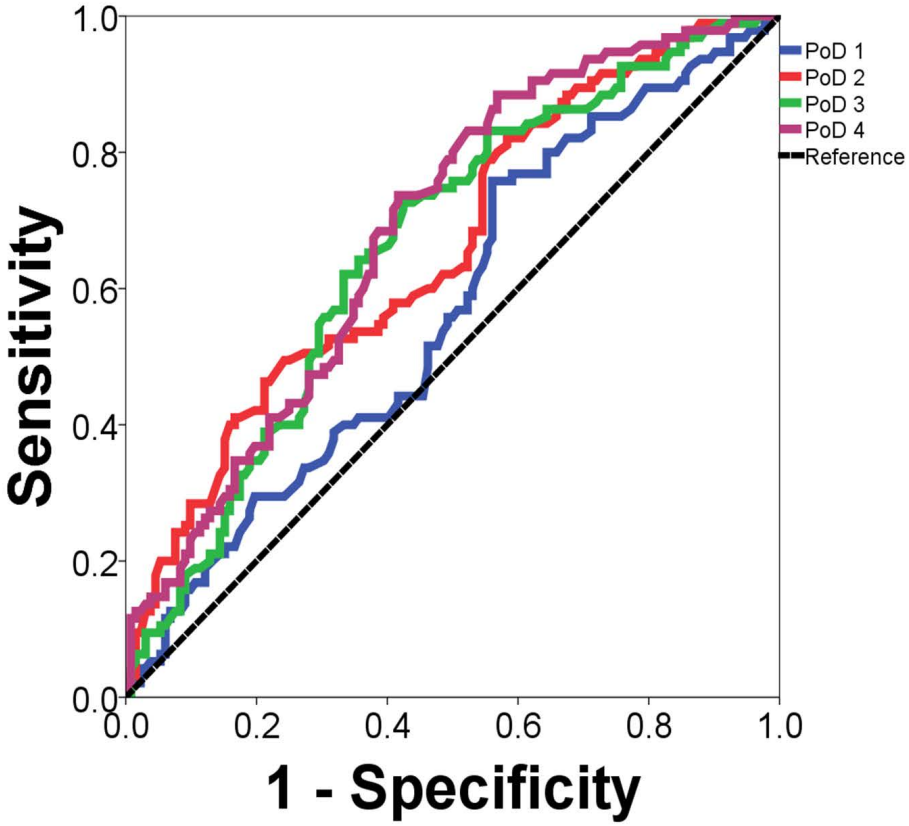
Supplementary Table 3. Logistic regression analysis of pre-operative factors, intra-operative factors and serum markers as predictors of PoD_2 serum CRP ≥ 180mg/L (n = 230).

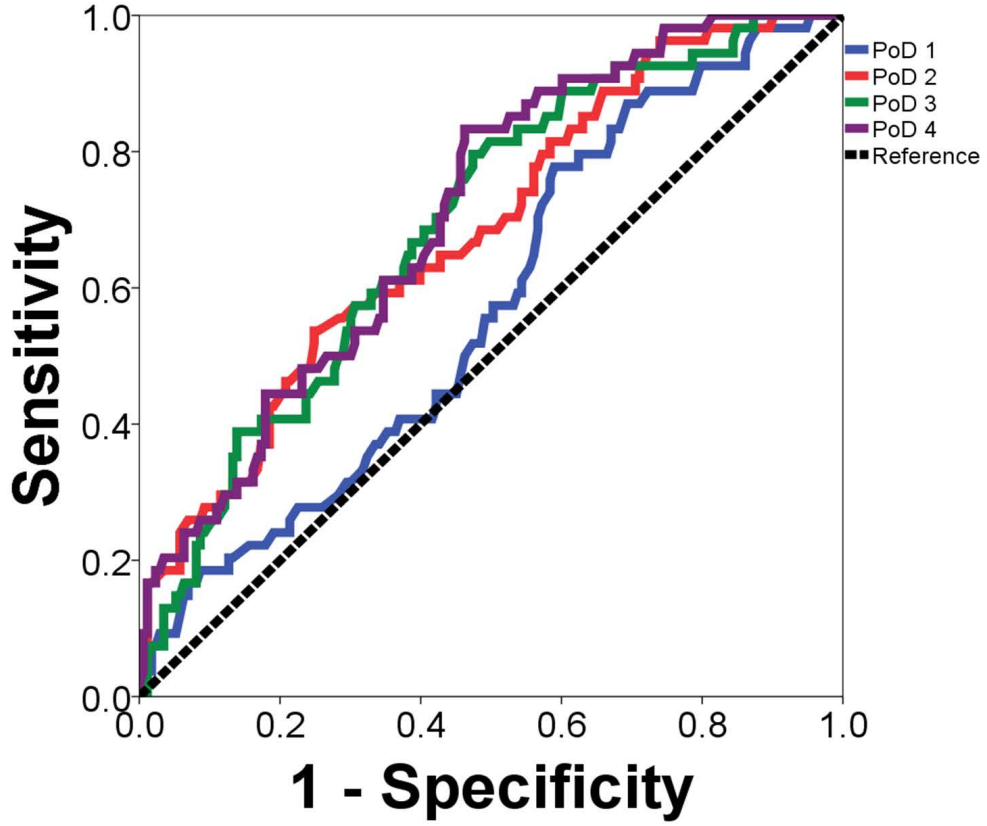
		Univariable			Multivariable		
Variable	**n (%)**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Preoperative Factors							
Age (years)							
≤ 60	100 (43.5)						
>60	130 (56.5)	0.80	0.45 – 1.40	0.434			
Sex							
Female	79 (34.4)						
Male	151 (65.6)	1.54	0.86 – 2.73	0.143			
BMI (kg/m^2)							
< 25	97 (42.2)						
≥ 25	126 (54.8)	2.06	1.16 – 3.66	**0.014**			
Smoking							
No	137 (59.6)						
Yes	71 (30.9)	1.21	0.64 – 2.29	0.559			
POSSUM Score							
≤ 16	114 (49.6)						
>16	97 (42.2)	1.48	0.82 – 2.67	0.197			
Bilirubin (mmol/L)							
≤ 250	197 (85.7)						
> 250	33 (14.3)	0.32	0.15 – 0.69	**0.003**			
Preoperative Biliary Drainage							
No	129 (56.1)						
Yes	101 (43.9)	1.40	0.79 – 2.46	0.248			
ASA							
I - II	165 (71.7)						
III - IV	37 (16.1)	0.675	0.32 – 1.41	0.294			
Intraoperative Factors							
Vein Resection							
No	193 (83.9)						
Yes	37 (16.1)	0.723	0.35 – 1.50	0.386			
Pancreatic Texture							
Hard	99 (43.0)						
Soft	94 (40.9)	2.51	1.33 – 4.74	**0.005**			
Pancreatic Duct Diameter (mm)							
> 3	142 (61.8)						
≤ 3	81 (35.2)	3.41	1.72 – 6.74	**< 0.001**	**2.53**	**1.12 – 5.68**	**0.025**
Pancreatic Anastomosis							
Pancreaticogastrostomy	50 (21.7)						
Pancreaticojejunostomy	175 (76.1)	0.61	0.30 – 1.24	0.172			
Estimated blood loss (ml)							
≤ 1450	121 (56.3)						
>1450	94 (43.7)	1.50	0.82 – 2.72	0.187			
Pathology							
PDAC/ Chronic Pancreatitis	100 (43.5)						
Other	130 (56.5)	2.74	1.55 – 4.85	**0.001**			
Serum Markers							
PoD_0 Serum Amylase (IU/L)							
< 130	123 (57.5)						
≥ 130	91 (42.5)	4.82	2.38 – 9.76	**< 0.001**	**3.49**	**1.53 – 7.93**	**0.003**

Supplementary Table 4. The relationship between PoD_0 serum amylase, PoD_2 serum CRP, and postoperative complications after pancreaticoduodenectomy

Variable	Low Risk	Intermediate Risk		High Risk	
n = 214	**n (%) 52 (22.6)**	**n (%) 83 (38.8)**	***P*** [2]	**n (%) 79 (36.9)**	***P*** [3]
Pancreatic Consistency					
Hard	40 (76.9)	49 (59.0)		15 (19.0)	
Soft	12 (23.1)	34 (41.0)	0.034	64 (81.0)	<0.001
Pancreatic Duct Size (mm)					
> 3	42 (82.4)	52 (63.4)		25 (31.6)	
≤ 3	9 (17.6)	30 (36.6)	0.020	54 (68.4)	<0.001
Estimated Blood Loss (ml)					
< 1450	33 (63.5)	48 (57.8)		43 (54.4)	
≥ 1450	19 (36.5)	35 (42.2)	0.517	36 (45.6)	0.664
Pathology					
PDAC/Chronic pancreatitis	31 (59.6)	39 (47.0)		20 (25.3)	
Other	21 (40.4)	44 (53.0)	0.155	59 (74.7)	0.004
Pancreas Specific Complications[1]					
Grade 0 – I	45 (86.5)	54 (65.1)		27 (34.2)	
Grade II – V	7 (13.5)	29 (34.9)	0.006	52 (65.8)	<0.001
Postoperative Pancreatic Fistula[1]					
Grade 0 – I	51 (98.1)	67 (80.7)		44 (55.7)	
Grade II – V	1 (1.9)	16 (19.3)	0.003	35 (44.3)	0.001
Post Pancreatectomy Haemorrhage[1]					
Grade 0 – I	51 (98.1)	74 (89.2)		65 (82.3)	
Grade II – V	1 (1.9)	9 (10.8)	0.055	14 (17.7)	0.211
Intra-abdominal Collection[1]					
Grade 0 – I	46 (88.5)	65 (78.3)		40 (50.6)	
Grade II – V	6 (11.5)	18 (21.7)	0.135	39 (49.4)	<0.001
Cardiorespiratory Complications[1]					
Grade 0 – I	46 (88.5)	69 (83.1)		57 (72.2)	
Grade II – V	6 (11.5)	14 (16.9)	0.398	22 (27.8)	0.094
Wound Complications[1]					
Grade 0 – I	47 (90.4)	72 (86.7)		63 (79.7)	
Grade II – V	5 (9.6)	11 (13.3)	0.526	16 (20.3)	0.234
Admissions to Critical Care (episodes)					
1	49 (94.2)	67 (80.7)		53 (67.1)	
>1	3 (5.8)	16 (19.3)	0.029	26 (32.9)	0.048
Invasive Intervention					
No	48 (92.3)	66 (79.5)		50 (63.3)	
Yes	4 (7.7)	17 (20.5)	0.047	29 (36.7)	0.022
Reoperation					
No	50 (96.2)	75 (90.4)		61 (77.2)	
Yes	2 (3.8)	8 (9.6)	0.213	18 (22.8)	0.023
Length of Postoperative Hospital Stay (days)					
≤ 15	45 (86.5)	57 (68.7)		37 (46.8)	
> 15	7 (13.5)	26 (31.3)	0.019	42 (53.2)	0.005
Length of Critical Care Stay (days)					
≤ 7	39 (75.0)	43 (51.8)		30 (38.0)	
> 7	13 (25.0)	40 (48.2)	0.007	49 (62.0)	0.084
Readmission					
No	46 (88.5)	64 (77.1)		60 (75.9)	
Yes	6 (11.5)	19 (22.9)	0.115	19 (24.1)	1.000
Mortality (90-day)					
No	52 (100.0)	81 (97.6)		72 (91.1)	
Yes	0	2 (2.4)	0.261	7 (8.9)	0.074

[1] Refers to Dindo-Clavien classification of postoperative complications.
[2] Intermediate compared to Low Risk patients.
[3] High compared to Intermediate Risk patients.
N = 214, 16 patients did not have PoD_0 serum amylase measured.
Low Risk: PoD_0 serum amylase < 130 IU/L AND PoD_2 serum CRP <180 mg/L
Intermediate Risk: PoD_0 serum amylase <130 IU/L AND PoD_2 serum CRP ≥180 mg/L **OR** PoD_0 serum amylase ≥ 130 IU/L AND PoD_2 <180 mg/L





Postoperative Day (PoD)	Threshold value (mg/L)	Area Under the Curve (AUC)	95% CI	Sensitivity	Specificity	*P*
1	102	0.576	0.50 – 0.65	76.1	43.9	0.052
2	**179**	**0.648**	**0.58 – 0.72**	**81.5**	**40.3**	**<0.001**
3	158	0.667	0.60 – 0.74	82.6	45.0	<0.001
4	129	0.693	0.63 – 0.76	77.2	47.3	<0.001

(A) Clinically Relevant Pancreas Specific Complications

Postoperative Day (PoD)	Threshold value (mg/L)	Area Under the Curve (AUC)	95% CI	Sensitivity	Specificity	*P*
1	98.50	0.573	0.49 – 0.66	79.60	37.40	0.106
2	**230.50**	**0.682**	**0.60 – 0.76**	**61.1**	**61.9**	**<0.001**
3	204.50	0.692	0.62 – 0.77	63.0	62.4	<0.001
4	134.50	0.708	0.64 – 0.78	83.4	53.8	<0.001

(B) Clinically Relevant Postoperative Pancreatic Fistula

Figure 1. ROC analysis examining the diagnostic accuracy of serial measurements of serum CRP in predicting clinically relevant (A) pancreas-specific complications and (B) postoperative pancreatic fistula after pancreaticoduodenectomy (n = 230).

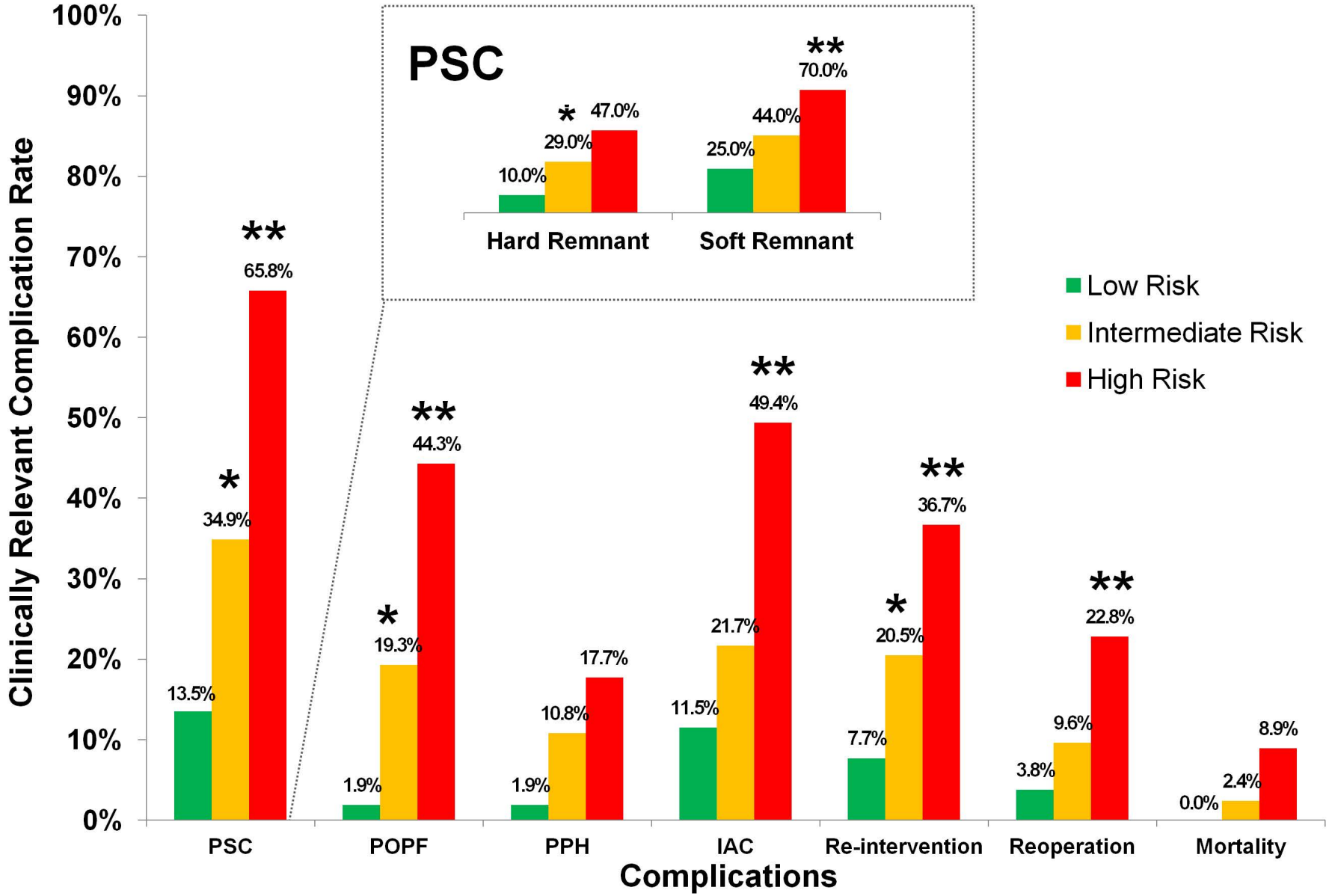


Figure 2. Risk stratification for clinically relevant pancreas-specific complications after pancreaticoduodenectomy utilising PoD_0 serum amylase and PoD_2 serum CRP.
Low Risk: PoD_0 serum amylase < 130 IU/L AND PoD_2 serum CRP <180 mg/L.
Intermediate Risk: PoD_0 serum amylase <130 IU/L AND PoD_2 serum CRP ≥180 mg/L or PoD_0 serum amylase ≥ 130 IU/L AND PoD_2 serum CRP <180 mg/L
High Risk: PoD_0 serum amylase ≥ 130 IU/L AND PoD_2 serum CRP ≥180 mg/L
PSC – Pancreas-specific complications, **POPF** – Postoperative pancreatic fistula, **PPH** – Post-pancreatectomy haemorrhage, **IAC** – Intra-abdominal collection
* - ***P*** < 0.05 Intermediate Risk vs. Low Risk. ** - ***P*** < 0.05 High Risk vs. Intermediate Risk.